Remarks

Summary of Invention

The invention is drawn to a method of enhancing bone density or formation (claims 1-12 17-18 and 34-36), a viral vector (claims 19-21, 26, and 37-43), and a bone graft (claims 22-23, 25, and 27-33).

Discussion of Office Action

The Office Action rejects claims 1-12, 17-21, and 26 as allegedly not enabled.

Discussion of Claim Amendments

Claims 4, 26, and 27 are amended to specify the identity of the angiogenic factor. New claims 28, 36, and 37 contain subject matter deleted from claims 4, 26, and 27 herein.

Claim 21 is amended to cure a grammatical error.

New claims 34 and 35 are added to recite that the first and second nucleic acids delivered in claims 1 and 6 are delivered via adenoviral vectors. These claims are supported in the specification, for example, at page 5, line 28, through page 6, line 20.

New claims 29-33 and 38-43 specify the identity of the osteogenic factor. These claims are supported in the specification, for example, on page 3, line 18 through page 4, line 2.

These amendments add no new matter to the application. For the convenience of the Examiner, a marked-up illustration of the claims as amended is attached hereto, as is the text of all claims pending upon entry of the amendments set forth herein.

Discussion of Enablement Rejection - 35 U.S.C. § 112, first paragraph

The Office Action rejects claims 1-12, 17-21, and 26 under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. The basis for this rejection is the Office Action's allegation that the application does not teach how to use vectors other than adenoviral vectors. The Office appears to be attempting to limit the scope of the claims to only the vector system employed in the Examples set forth in the specification. This ignores not only the remainder of the specification, which must be considered, but also the teachings known to those of skill in the art.

When considered in light of the art as a whole, which is the proper inquiry here, the specification adequately teaches those of skill in the art to how to use vector systems apart from adenoviral vector systems. In this regard, the specification specifically identifies that several vector systems that can be employed (see, e.g., page 5, line 28, through page 6, line 20). Furthermore, this passage cites to enabling treatises, peer-reviewed publications, published patent applications, and issued U.S. Patents (which are

presumed to be enabling), each of which has been incorporated by reference into the specification (see page 11, lines 24-29). It is urged that, when read in light of the art as a whole (including the incorporated references), the specification adequately teaches those of skill in the art to use vectors in addition to adenoviral vectors. Accordingly, the rejection under Section 112, first paragraph, should be withdrawn.

Additional Comments

Notwithstanding the rejection, the Office Action concedes that the specification is enabling for administering either (i) an adenoviral vector encoding VEGF operably linked to a promoter or (ii) an adenoviral vector encoding VEGF and a second osteogenic protein each of which is operably linked to a promoter, to a bone or within a tissue immediately surrounding the bone, whereby bone density or formation is enhanced. The Office Action further acknowledges that claim 20 is drawn to allowable subject matter. Accordingly, new claims 34 and 35 also should be indicated as being allowable, even if the rejection is maintained.

The Office Action further stated that claims 22, 23, 25, and 27, drawn to a bone graft, are allowable. New claims 28-33, which further specify the identity of the angiogenic and osteogenic factors, also should be considered allowable.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

M. Daniel Hefner, Reg. No. 41826
One of the Attorneys for Applicant(s)
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 North Stetson
Chicago, Illinois 60601-6780
(312) 616-5600 (telephone)
(312) 616-5700 (facsimile)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Crystal et al.

Art Unit: 1632

Application No. 09/629,074

Examiner: Anne-Marie Baker

Filed: July 31, 2000

For: METHOD OF ENHANCING BONE DENSITY

ILLUSTRATION OF AMENDMENTS FILED ON DECEMBER 20, 2002

Amendments to the claims:

4. The method of claim 1, wherein the vascular endothelial growth factor is $VEGF_{121}$ [~~or $VEGF_{165}$~~].

21. The viral vector of claim 19, which is deficient in at least one essential gene function.

26. The viral vector of claim 19, wherein the vascular endothelial growth factor is $VEGF_{121}$ [~~or $VEGF_{165}$~~].

27. The bone graft of claim 22, wherein the vascular endothelial growth factor is $VEGF_{121}$ [~~or $VEGF_{165}$~~].

28. The bone graft of claim 22, wherein the vascular endothelial growth factor is $VEGF_{165}$.

29. The bone graft of claim 22, wherein the osteogenic protein is selected from the group consisting of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7 and BMP-8.

30. The bone graft of claim 22, wherein the osteogenic protein is TGF-b1.

31. The bone graft of claim 22, wherein the osteogenic protein is BMP-2.

32. The bone graft of claim 22, wherein the osteogenic protein is MK.

33. The bone graft of claim 22, wherein the osteogenic protein is HBNF.

34. The method of claim 1, wherein the first nucleic acid is administered via an adenoviral vector.

35. The method of claim 6, wherein the second nucleic acid is administered via an adenoviral vector.

36. The method of claim 1, wherein the vascular endothelial growth factor is $VEGF_{165}$.

37. The viral vector of claim 19, wherein the vascular endothelial growth factor is $VEGF_{165}$.

38. The viral vector of claim 19, wherein the osteogenic protein is selected from the group consisting of a bone morphogenic protein (BMP), a transforming growth factor (TGF), a latent TGF binding protein (LTBP), latent membrane protein-1 (LMP-1), a heparin-binding neurotrophic factor (HBNF), growth and differentiation factor-5 (GDF-5), a parathyroid hormone (PTH), a fibroblast growth factor (FGF), an epidermal growth factor (EGF), a platelet-derived growth factor (PDGF), an insulin-like growth factor, a growth factor receptor, a cytokine, a chemotactic factor, a LIM mineralization protein (LMP), a leukemia inhibitory factor (LIF), a hedgehog protein, and midkine (MK).

39. The viral vector of claim 19, wherein the osteogenic protein is selected from the group consisting of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7 and BMP-8.

40. The viral vector of claim 19, wherein the osteogenic protein is TGF-b1.

41. The viral vector of claim 19, wherein the osteogenic protein is BMP-2.

42. The viral vector of claim 19, wherein the osteogenic protein is MK.

43. The viral vector of claim 19, wherein the osteogenic protein is HBNF.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Crystal et al.

Art Unit: 1632

Application No. 09/629,074

Examiner: Anne-Marie Baker

Filed: July 31, 2000

For: METHOD OF ENHANCING BONE DENSITY

CLAIMS PENDING UPON ENTRY OF THE AMENDMENTS OF DECEMBER 20, 2002

1. A method for enhancing bone density or formation, the method comprising administering to at least one first cell associated with a region of a bone at least one first nucleic acid encoding a vascular endothelial growth factor, such that the first nucleic acid is expressed in the cell to produce the vascular endothelial growth factor, whereby bone density or formation is enhanced within the region, wherein the first cell is within the bone or within a tissue immediately surrounding the bone.

2. The method of claim 1, wherein at least one of the nucleic acids is exposed to at least one cell in vivo in the region of the bone.

3. The method of claim 1, wherein at least one of the nucleic acids is exposed to at least one cell ex vivo, which is then delivered in vivo to the region of the bone.

4. The method of claim 1, wherein the vascular endothelial growth factor is $VEGF_{121}$.

5. The method of claim 1, wherein the vascular endothelial growth factor is selected from the group consisting of $VEGFA_{138}$, $VEGFA_{162}$, $VEGF_{182}$, $VEGF_{189}$, VEGF2, and VEGF-C.

6. The method of claim 1, further comprising administering to at least one second cell associated with the region at least one second nucleic acid encoding at least one osteogenic protein, such that the second nucleic acid is expressed in the cell to produce the osteogenic protein, wherein the second cell is within the bone or within a tissue immediately surrounding the bone.

7. The method of claim 6, wherein the osteogenic protein is selected from the group consisting of a bone morphogenic protein (BMP), a transforming growth factor (TGF), a latent TGF binding protein (LTBP), latent membrane protein-1 (LMP-1), a heparin-binding neurotrophic factor (HBNF), growth and differentiation factor-5 (GDF-5), a parathyroid hormone (PTH), a fibroblast growth factor (FGF), an epidermal growth

factor (EGF), a platelet-derived growth factor (PDGF), an insulin-like growth factor, a growth factor receptor, a cytokine, a chemotactic factor, a LIM mineralization protein (LMP), a leukemia inhibitory factor (LIF), a hedgehog protein, and midkine (MK).

8. The method of claim 6, wherein the osteogenic protein is selected from the group consisting of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7 and BMP-8.

9. The method of claim 6, wherein the osteogenic protein is TGF-b1.

10. The method of claim 6, wherein the osteogenic protein is BMP-2.

11. The method of claim 6, wherein the osteogenic protein is MK.

12. The method of claim 6, wherein the osteogenic protein is HBNF.

17. The method of claim 6, wherein the first cell and the second cell are the same cell.

18. The method of claim 6, wherein the first nucleic acid and the second nucleic acid are the same nucleic acid.

19. A viral vector comprising at least one first nucleic acid encoding a vascular endothelial growth factor and at least one second nucleic acid encoding at least one osteogenic protein.

20. The viral vector of claim 19, which is an adenoviral vector.

21. The viral vector of claim 19, which is deficient in at least one essential gene function.

22. A bone graft comprising at least one first cell having at least one first exogenous nucleic acid encoding a vascular endothelial growth factor and at least one second cell having at least one second nucleic acid encoding at least one osteogenic protein.

23. The bone graft of claim 22, wherein the osteogenic protein is selected from the group consisting of a bone morphogenic protein (BMP), a transforming growth factor (TGF), a latent TGF binding protein (LTBP), latent membrane protein-1 (LMP-1), a heparin-binding neurotrophic factor (HBNF), growth and differentiation factor-5 (GDF-5), a parathyroid hormone (PTH), a fibroblast growth factor (FGF), an epidermal growth factor (EGF), a platelet-derived growth factor (PDGF), an insulin-like growth factor (IGF), a growth factor receptor, a cytokine, a chemotactic factor, a LIM mineralization protein (LMP), a leukemia inhibitory factor (LIF), a hedgehog protein, and midkine (MK).

25. The bone graft of claim 22, which is an allograft.

26. The viral vector of claim 19, wherein the vascular endothelial growth factor is $VEGF_{121}$.

27. The bone graft of claim 22, wherein the vascular endothelial growth factor is $VEGF_{121}$.

28. The bone graft of claim 22, wherein the vascular endothelial growth factor is $VEGF_{165}$.

29. The bone graft of claim 22, wherein the osteogenic protein is selected from the group consisting of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7 and BMP-8.

30. The bone graft of claim 22, wherein the osteogenic protein is TGF-b1.

31. The bone graft of claim 22, wherein the osteogenic protein is BMP-2.

32. The bone graft of claim 22, wherein the osteogenic protein is MK.

33. The bone graft of claim 22, wherein the osteogenic protein is HBNF.

34. The method of claim 1, wherein the first nucleic acid is administered via an adenoviral vector.

35. The method of claim 6, wherein the second nucleic acid is administered via an adenoviral vector.

36. The method of claim 1, wherein the vascular endothelial growth factor is $VEGF_{165}$.

37. The viral vector of claim 19, wherein the vascular endothelial growth factor is $VEGF_{165}$.

38. The viral vector of claim 19, wherein the osteogenic protein is selected from the group consisting of a bone morphogenic protein (BMP), a transforming growth factor (TGF), a latent TGF binding protein (LTBP), latent membrane protein-1 (LMP-1), a heparin-binding neurotrophic factor (HBNF), growth and differentiation factor-5 (GDF-5), a parathyroid hormone (PTH), a fibroblast growth factor (FGF), an epidermal growth factor (EGF), a platelet-derived growth factor (PDGF), an insulin-like growth factor, a growth factor receptor, a cytokine, a chemotactic factor, a LIM mineralization protein (LMP), a leukemia inhibitory factor (LIF), a hedgehog protein, and midkine (MK).

39. The viral vector of claim 19, wherein the osteogenic protein is selected from the group consisting of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7 and BMP-8.

40. The viral vector of claim 19, wherein the osteogenic protein is TGF-b1.

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